Probability of target attainment of ceftolozane/tazobactam among adult patients with hospital-acquired pneumonia/ventilator-associated pneumonia secondary to *Pseudomonas aeruginosa* in Latin America

Aline Okuma[1]; Thales Polis[1]; Jacqueline Pavia[3]; Gustavo Mizuno[1]; Jacqueline Ferrari[1]; Prachi Wickremasingha[2]; C. Andrew DeRyke[2]

[1]MSD Brazil, Sao Paulo, Brazil; [2]Merck & Co., Inc., Rahway, NJ, USA; [3]MSD Colombia, Bogota, Colombia

Background

- Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are common hospital-acquired infections that are associated with mortality rates as high as 50%[1-3]
- *Pseudomonas aeruginosa (Pa)* is a common cause of nosocomial pneumonia; resistance among traditionally used empiric agents is frequently observed[4]
- To improve patient outcomes, a heightened focus has been placed on evaluating the adequacy of recommended dosing regimens, particularly of beta-lactams
- Ceftolozane/tazobactam (C/T), a combination of a potent antipseudomonal cephalosporin (ceftolozane) with a beta-lactamase inhibitor (tazobactam), is primarily renally excreted, and requires dose adjustment based on renal function[4]
- The Phase 3 study ASPECT-NP demonstrated the efficacy and safety of 3 g of ceftolozane/tazobactam infused in 1 hour, every 8 h for 8 to 14 days for treatment of adults with HAP/VAP[4]
- We assessed the Probability of Target Attainment (PTA) of the ceftolozane/tazobactam 3g dosage, infused in 1 hour, every 8h, regimen in patients with HAP/VAP due to *Pseudomonas aeruginosa*, with an additional focus on carbapenem-resistant *Pa*, from Latin America

PopPK Models and subsequent Simulation of exposures to support Probability of Target attainment have been previously presented and published elsewhere [5]. In brief summary of this work:

- **Population Pharmacokinetic (PopPK) Modeling**
  - PopPK models describing plasma concentrations of ceftolozane and tazobactam in patients with HAP/VAP were developed based on a previously established 2-compartment model with first-order elimination[5,6]
  - The plasma C/T concentration data from 16 clinical studies, including ASPECT-NP, informed the plasma components of the popPK models
  - Pulmonary epithelial lining fluid (ELF) C/T concentration data from two phase 1 studies informed the ELF component of the popPK models; disposition of ceftolozane and tazobactam in ELF was described by a hypothetical link model with influx and elimination from the ELF compartment[6,7]
  - Among the covariates identified in the developed popPK models in patients with HAP/VAP, baseline creatinine clearance (CrCl) was a significant covariate on ceftolozane and tazobactam clearance; weight and pneumonia were covariates on ceftolozane and tazobactam volumes of distribution; pneumonia was a covariate on the influx and elimination rate constants for the ELF compartment
- **Simulations**
  - Virtual patients with paired weight and CrCl were randomly drawn from a large virtual population database constructed based on pivotal trials in the infectious disease area for each of the following renal function categories (n=1000 each): normal (CrCl ≥80 to <150 mL/min) and mild, moderate, and severe renal impairment (CrCl >50 to <80 mL/min, CrCl ≥30 to ≤50 mL/min, and CrCl ≥15 to ≤29 mL/min, respectively)
  - Ceftolozane and tazobactam concentration-time profiles in plasma and ELF were simulated using the popPK models in patients with HAP/VAP at 3 different dosing regimens, adjusted based on CrCl, administered via 1-hour infusion every 8 hours over a 14-day treatment duration:
  - Dosing regimen 1: 0.5 g/0.25 g C/T for patients with CrCl of ≥15 to ≤29 mL/min
  - Dosing regimen 2: 1 g/0.5 g C/T for patients with CrCl of ≥30 to ≤50 mL/min
  - Dosing regimen 3: 2 g/1 g C/T for patients with CrCl of >50 mL/min

Method

- Non duplicate *Pseudomonas aeruginosa* isolates from a respiratory source were collected as part of the SMART surveillance program from 36 sites in 10 Latin American countries during 2017-2020
- MICs were determined by broth microdilution and interpreted by CLSI criteria
- Ceftolozane and Tazobacatm concentration-time profiles were simulated in plasma and ELF following administration of the approved 3g (2g/1g) C/T dose (or equivalent dose adjusted based on renal function) administered by 1-hour infusion every 8 hours
- PTA was assessed using exposures derived from simulations. PTA in plasma and ELF was calculated using the PK/PD target of 30% *ƒ*T>MIC for Ceftolozane. Tazobactam does not contribute to the antipseudomonal activity therefore was not included in this analysis
- Additional ceftolozane ELF and plasma PTA assessments were conducted for ceftolozane at higher PK/PD targets of up to 50% *ƒ*T>MIC=4 µg/mL, which corresponds to a 2-log kill at the highest breakpoint for susceptible pathogens[8]

Results

- A total of 2,757 *Pseudomonas aeruginosa* isolates were collected, from 10 Latin America countries, of which 1208 (43.8%) were carbapenem nonsusceptible (**Table 1 and 2**)
- Ceftolozane/Tazobactam was active against 87.7% of all *Pa* and 73.4% of carbapenem nonsusceptible strains (**Table 2**)
- At ceftolozane/tazobactam doses of 2g/1g (CrCL>50mL/min); 1g/0.5g (30mL/min≤CrCL≤50mL/min), and 500mg/250mg (15mL/min≤CrCL≤29mL/min), steady-state ceftolozane plasma (**Figure 1A**) and ELF (**Figure 1B**) PTA was 100% and >99%, respectively, for isolates with an MIC at the *Pa* susceptibility breakpoint of 4 µg/mL. Ceftolozane plasma and ELF PTA remained above 90% up to an MIC of 16 µg/mL and 8 µg/mL
- At the recommended dosing regimens, using ceftolozane targets of 50% *ƒ*T>MIC, plasma and ELF PTA was >99% at an MIC of 4 µg/mL across renal categories at CrCl up to 150 mL/min (**Table 3**)

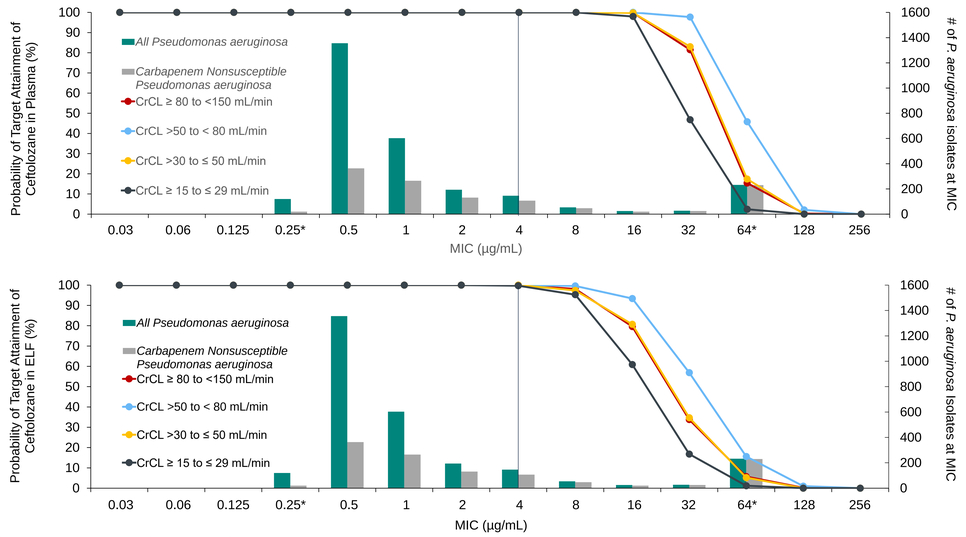
Table 1: Frequency of *P. aeruginosa* in HAP/VAP by country, n = 2,757

Country	Frequency	% of Total
Argentina	466	16.9%
Brazil	453	16.4%
Mexico	414	15.0%
Colombia	305	11.1%
Chile	297	10.8%
Panama	286	10.4%
Puerto Rico	172	6.2%
Venezuela	149	5.4%
Guatemala	129	4.7%
Ecuador	86	3.1%

Table 2. *P. aeruginosa* MIC distribution

MIC	≤ 0.25	0,5	1	2	4	8	16	32	≥ 64	
All *Pseudomonas aeruginosa*, n (%)	120 (4.4%)	1356 (49.0%)	603 (22.0%)	194 (7.0%)	146 (5.3%)	54 (2.0%)	25 (0.9%)	27 (1.0%)	232 (8.4%)	2757 (100%)
Carbapenem-nonsusceptible *Pseudomonas aeruginosa*, n (%)	20 (1.7%)	363 (30.0%)	265 (21.9%)	131 (10.8%)	107 (8.9%)	47 (3.9%)	20 (1.7%)	25 (2.1%)	230 (19%)	1208 (100%)

Figure 1. PTA at steady state in plasma (panel A) and ELF (panel B) for ceftolozane at a target of 30% *ƒ*T>MIC for virtual patients with HAP/VAP, by CrCl category[a], with *P. aeruginosa* MIC distributions among Latin America isolates



*MICs were truncated at ≥ 0.25 µg/mL and ≤ 64 µg/mL
Solid horizontal line on plots represents 90% PTA; vertical line in panels A and B represents MIC=4 µg/mL.
[a]CrCl for all patients was calculated using the Cockcroft and Gault formula.[9]
CrCl, creatinine clearance; ELF, epithelial lining fluid; *ƒ*T, free drug concentration during the dosing interval; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PTA, probability of target attainment.

Discussion

- At C/T doses of 2g/1g (CrCL>50mL/min); 1g/0.5g (30mL/min≤CrCL≤50mL/min), and 500mg/250mg (15mL/min≤CrCL ≤29mL/min), steady-state ceftolozane plasma and ELF PTA was 100% and >99%, respectively, for isolates with an MIC at the *Pa* susceptibility breakpoint of 4 µg/mL. While *f*T>MIC of 30% is the established pharmacodynamic target (PD) for these dosing regimens (based on 1-log kill in a mouse infection model [**Figures 1A and B**]), exposures were also adequate to meet a higher pharmacodynamic target of 50% *f*T>MIC target (corresponding to a 2-log kill in a mouse infection model [**Table 3**])[5]
- The exposures of the virtual population used in the PTA analysis is based on PopPK used to support the HAP/VAP indication in adults which included very few Latin American participants. However, race was evaluated as a covariate in the PopPK analysis where race was categorized as white, Japanese, and other.[10] Race was not considered a covariate related to PK exposures of Ceftolozane

Table 3. Percentage of HAP/VAP Patients Achieving a Ceftolozane Target of 50% *ƒ*T>MIC at an MIC = 4 µg/mL

	Ceftolozane Target of 50% *ƒ*T>MIC=4 µg/mL	
	Plasma	ELF
CrCl ≥15 to ≤29 mL/min	100	99.7
CrCl ≥30 to ≤50 mL/min	100	100
CrCl >50 to <80 mL/min	100	100
CrCl ≥80 to <150 mL/min	100	100

CrCl, creatinine clearance; ELF, epithelial lining fluid; *ƒ*T>CT, percent of the dosing interval during which the free drug concentration exceeds the threshold concentration; *ƒ*T>MIC, percent of the dosing interval during which the free drug concentration exceeds the minimum inhibitory concentration; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; MIC, minimum inhibitory concentration.[5]

Conclusion

The approved dosage regimen of C/T 3g for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, administered over 1 hour, every 8 hours (or equivalent dose adjusted based on renal function), resulted in high plasma and ELF PTAs sufficient to cover the vast majority of circulating *P. aeruginosa* present in Latin America, including carbapenem resistant strains.

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Disclosure

AO, TP, JP, GM, JF, PW and AD are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time of the study.

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